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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/463,494	07/25/2000	MANFRED T. REETZ	STUDIEN-268-	6396

7590 08/18/2004

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EXAMINER

PATTERSON, CHARLES L JR

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 08/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/463,494

Applicant(s)

REETZ ET AL.

Examiner

Charles L. Patterson, Jr.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 June 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 42-47 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 42-47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 07 January 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 42-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Nakanishi, et al. (N), Hirose, et al. (U-2) or Krainev, et al. (V-2) in view of Williams, et al. (A), Zhou, et al. (U), Leung, et al. (V), Cadwell, et al. (W) and Shinkai, et al. (X). (W-1). This rejection is repeated for the reasons given in the last action. Applicants arguments have been carefully considered but do not overcome the instant rejection.

Applicant argue that the examiner has not addressed the limitation in claims 42 and 45 as to adjusting the Mg^{2+} , Mn^{2+} or the deoxynucleotide concentration and the number of cycles of the reaction.

In Williams, et al. it is stated in column 1, lines 43-52 that "[in] an improved variation...the target sequence of interest is copied under conditions which further reduce the fidelity of DNA synthesis...by the addition of the co-factor manganese and by the use of high concentrations of magnesium and relevant deoxynucleoside triphosphates". In column 4, lines 57-64 it is stated that "there is a substantially linear correlation between the mutation frequency and the number of PCT cycles performed...[in] addition, further influence on mutation frequency may be effected by alteration of the concentration of deoxynucleoside triphosphates".

In the paragraph columns 1 and 2 of page 14 of Leung, et al. it is stated that "[t]he fidelity of DNA synthesis by Taq DNA polymerase is reduced in the presence of Mn^{2+} ". In the second full paragraph of column 2 on that page

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it is stated that "it is possible to increase the overall frequency of mutation to 2% by using dGTP/dATP ratio of five and adding Mn^{2+} into the reaction... [and that] [i]t is conceivable that one can increase the frequency of mutations even further by repeating the whole PCR cycle many times". Zhou, et al. refers to Leung, et al. in line 5.

Cadwell, et al. in column 2 of page 31 refers to Leung, et al. on line 2 and then states on lines 6-9 that "increased concentrations of dGTP, dCTP, and dTTP relative to dATP results in substantial excess $A \rightarrow G$ and $T \rightarrow C$ changes". In the first full paragraph on that page it is stated that "[a]ddition of 0.5 mM $MnCl_2$...is expected to have a significant mutagenic effect", "[a]n obvious way to increase the overall error rate of the PCR would be to carry out more reaction cycles", and "it has been shown that the error rate of the PCT is enhanced by increasing the concentration of $MgCl_2$ ".

Shinkai, et al. refers to Cadwell, et al. in the first full paragraph of column 1 on page 916.

It is maintained that the secondary references do teach adjusting the Mg^{2+} , Mn^{2+} or the deoxynucleotide concentration and the number of cycles of the reaction in order control the number of mutations, as outlined *supra*.

Stemmer and Zhang. et al. are hereby dropped from the rejection as they teach DNA shuffling and not PCR to introduce random mutagenesis.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the


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THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charles L. Patterson, Jr., PhD, whose telephone number is 571-272-0936. The examiner can normally be reached on Monday - Friday from 7:30 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Charles L. Patterson, Jr.
Primary Examiner
Art Unit 1652

Patterson
August 9, 2004